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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,578	03/09/2001	Patrick Hwu	2026-4341	6841

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,578	HWU ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,7,8,10,11,40,41,44-61 and 71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7,8,10,11,40,41,44-61 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 6 and 62-70 have been cancelled. Claim 71 has been added. Claims 1, 3, 4, 7, 8, 10, 11, 40, 41, 44-61 and 71 are pending and under consideration in the instant office action.

Applicant's arguments filed 6-29-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 1, 3, 4, 7, 8, 10, 11, 40, 41, 44-61 and 71 are under consideration in the instant office action.

Claim 1 is under consideration in the instant office action as it relates to a T lymphocyte having i) a recombinant MOv-γ receptor or a recombinant T-cell receptor (TCR) that reacts with an ovarian tumor antigen, and ii) an "endogenous" TCR that reacts with a cell that is allogeneic to the lymphocyte.

Claim 11 is under consideration as it relates to a lymphocyte having i) a TCR that reacts with a cell that is allogeneic to the lymphocyte, and ii) an MOv-γ receptor that reacts with an ovarian tumor antigen.

Claim 40 is under consideration as it relates to a pharmaceutical composition comprising lymphocytes having i) a recombinant MOv-γ receptor reactive with an

ovarian tumor antigen, and ii) an "endogenous" TCR that reacts with a cell that is allogeneic to the lymphocyte.

Claim 41 is under consideration as it relates to a method of preparing lymphocytes having dual specificity by i) contacting lymphocytes with a cell that is allogeneic to the lymphocyte, and ii) transducing the lymphocyte with an MOv-γ that reacts with an ovarian tumor antigen.

Specification

The status of application 08/547263, cited on pg 17, line 5, will need to be updated as necessary.

Claim Objections

The phrase "an endogenous T-cell receptor reactive with a cell, which cell is allogeneic to the lymphocyte" in claims 1, 11, 40 is objectionable. The phrase "a cell, which cell is" should be --a cell that is-- to be more clear.

Claim Rejections - 35 USC ' 112

I. Claims 1, 3, 4, 7, 8, 10, 11, 40, 41, 44-61 remain rejected and claim 71 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The scope of lymphocytes having a second receptor that recognizes any cell that is allogeneic to the lymphocyte is new matter (1, 11, 40, 41). Applicants point to pg 11, lines 1-12, which teach the antigen to which the T-cell receptor reacts, including a "strong antigen", e.g. an alloantigen on an allogeneic cell. Applicants point to Examples 3-9 and 11. Applicants' arguments are not persuasive. Examples 3-9 and 11 only teach stimulating the cells with PBMC and determining if the cells recognize allogeneic PBMC (Fig. 9). The specification does not teach the receptor will recognize any allogeneic cell as broadly claimed.

The phrase "dual antigen specificity" in claim 41 has been deleted. The phrase "dual specificity" as amended in claim 41 has support on pg 11, ¶ 41.

The T lymphocyte having two receptors comprising 1) an MOv-γ receptor, and 2) an endogenous receptor that reacts with a splenocyte, dendritic cell, B-cell or peripheral blood cell that is allogeneic to the lymphocyte (claims 46, 50, 56 and 58) remains new matter. Applicants argue support for the claims is found on pg 29-37 and pg 39-43. Applicants' argument is not persuasive. Pointing to 14 pages of text without explanation is not considered a substantive argument. However, the text has been reviewed and support cannot be found. Applicants point to pg 30, ¶ 79. Applicants' argument is not persuasive. Pg 30, ¶ 79 teaches administering "dual specificity allogeneic/Mov-γ T cells" into a mouse followed optionally by allogeneic splenocytes, then challenged with tumor cells. The results show tumor growth but do not show reaction with allogeneic

splenocytes. The specification does not teach the "dual specificity allogeneic/ MOv-γ T cells" had an "endogenous T-cell receptor reactive with" the splenocytes or that the "dual specificity allogeneic/ MOv-γ T cells" reacted with the splenocytes at all. Applicants point to pg 35, ¶ 83. Applicants' argument is not persuasive. Pg 35, ¶ 83 teaches stimulating PBMC with allogeneic PBMC, B-cells or dendritic cells. The specification does not teach the PBMC had an "endogenous T-cell receptor reactive with" the splenocytes or that the PBMC reacted with the PBMC, B-cells or dendritic cells as claimed.

II. Claims 1, 3, 4, 7, 8, 10, 11, 40, 41, 44-61 remain rejected and claim 71 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The "chimeric receptor reactive with a tumor antigen" lacks written description (1, 11, 40, 41). An adequate written description of a chimeric receptor requires a description of the nucleic acid sequence encoding the chimeric receptor because the protein is made by genetic modification. Adequate written description of a nucleic acid sequence encoding a chimeric receptor that recognizes tumor antigens requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to

define DNA solely by its principal biological property, i.e. recognizing tumor antigen because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property.

The only chimeric receptor taught in the specification that recognizes a tumor antigen as in claims 1, 11, 40 and 41 is the MOv-γ receptor. The specification does not teach the nucleic acid sequence of antibody or T-cell receptor fragments that recognize tumor antigens. The specification does not teach how the MOv-γ receptor was made so that other chimeric receptors having equivalent structures and functions could be made. The specification does not correlate the nucleic acid sequences encoding antibody fragments used to create the MOv-γ receptor to any other nucleic acid sequences known in the art that encoded antibody fragments that recognized tumor antigens. The nucleic acid sequence encoding the MOv-γ receptor is one species in a multitude of possible "chimeric receptors" that recognize a tumor antigen and is not adequate written description for the genus which encompasses any type of receptor (e.g. antibody, T-cell receptor, insulin receptor, cholesterol receptor, etc.) that reacts with any type of tumor antigen (e.g. MART, CEA, FBP, etc).

Thus, claiming a lymphocyte having a chimeric receptor that recognizes a tumor antigen without teaching the nucleic acid sequence encoding the fragments that are essential to make the chimeric receptor is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims,

adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

Applicants argue the specification describes many chimeric receptors reactive with a tumor antigen, e.g. paragraphs 43-46 and 48-52. Applicants argue the chimeric receptor may have an antibody variable region joined to the Fc receptor chain "capable of mediating T-cell receptor signal transduction" or the "cytoplasmic region of CD28 from a T-cell or a similar region which can provide a T cell with co-stimulation signals" as described on pg 12, lines 4-11. Applicants' arguments are not persuasive. Paragraphs 43-46 and 48-52 (pg 11-17) do not teach the structure of such chimeric receptors or nucleic acids encoding them. Paragraph 43 (pg 12, lines 1-7) states "the chimeric receptor gene encodes sequences for T-cell receptors or parts thereof which recognize tumor associated antigens and/or function to translate extracellular/cytoplasmic signal to intracellular activities in T-cells. One example of such a chimeric receptor gene encodes a single chain variable region from a monoclonal antibody joined to the Fc receptor chain capable of mediating T-cell receptor signal transduction." This "one example" functions "to translate extracellular/cytoplasmic signal to intracellular activities in T-cells" and does not recognize tumor antigens as claimed. Paragraph 43 (pg 12, lines 1-7) also states the chimeric receptor may also "comprise an antibody variable region joined to the cytoplasmic region of CD28 from a T cell or a similar region which can provide a T cell with co-stimulation signals." This chimeric receptor functions "to translate extracellular/cytoplasmic signal to intracellular

activities in T-cells" and does not recognize tumor antigens as claimed. Most importantly, the specification does not teach the structure of antibody variable regions used in the chimeric receptors described on pg 12, lines 4-11, that recognizing tumors as claimed.

Applicants argue the specification teaches a chimeric receptor may have an alpha, beta, or gamma chain of the IL-2 receptor (paragraph 44, pg 12, lines 12-15). Applicants' argument is not persuasive. The specification does not teach the structure of any such proteins that react with tumors or the nucleic acids encoding them.

None of the chimeric proteins in paragraphs 45, 46 or 48-52 recognize tumor antigen as claimed. Paragraphs 45, 46 and 48-52 do not describe the specific protein or protein fragments that recognize tumor antigen used in making the chimeric receptor or the nucleic acids encoding them.

Applicants argue there is no basis for requiring disclosure of complete DNA sequences when claiming DNA sequences because the specification amply describes the claimed invention without the need to provide any particular DNA sequences (pg 9 of response filed 6-28-04. Applicants' argument is not persuasive. In this case, the specification does not adequately describe the structure of any proteins that recognize tumor antigens on pg 12-17 other than MOv-γ. Therefore, the specification does not adequately describe the structure of nucleic acids used to make a chimeric receptor other than Mov-gamma.

Applicants' argue the examiner is requiring a reduction to practice. Applicants' argument is not persuasive. While written description may be met by reduction to

practice, the specification may also describe other proteins in the genus claimed. In this case, the MOv-γ chimeric receptor was known in the art (Hwu) and reduced to practice. Pg 12-17 does not adequately describe the structure of other antibodies that recognize tumor antigens or other chimeric receptors that recognize tumor antigens.

Claims 1, 3, 4, 7, 8, 10, 11, 40, 41 and 44-61 remain rejected and claim 71 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejection regarding the metes and bounds of claim 1 (whether the "chimeric receptor or a T-cell receptor, either of which is reactive with a tumor antigen" may also be the "endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte") has been withdrawn because applicants state claim 1 is limited to a cell with two receptors (pg 10, 2nd full ¶, of response filed 6-28-04) and because the specification, e.g. pg 17, ¶ 53, describes the lymphocytes of the invention as having two receptors.

The rejection regarding the term "endogenous T-cell receptor" has been withdrawn because applicants state claim 1 is limited to a cell with two receptors (pg 10, 2nd full paragraph, of response filed 6-28-04) and because pg 17, ¶ 53, describes the "T-cells whose endogenous TCR is directed to the strong antigen" as being "transduced with a chimeric receptor." The amendments to the claims do not make it clearer that the cells have two receptors.

Use of a "recombinant chimeric receptor" or a "recombinant T-cell receptor" that recognizes a tumor antigen together in claim 1 a) does not make sense. At first glance, it appears that the chimeric receptor is a species of the T-cell receptor because a chimeric receptor that recognizes a tumor antigen must be a T-cell receptor. But why would a species be listed with a genus instead of being used in a dependent claim to further limit the genus? One would then wonder if applicants were attempting to include two receptors having different scopes in claim 1 a). Thus, one of skill is left wondering whether the two receptors in claim 1 a) are related as species/genus or if they are two species having overlapping subject matter. The structural or functional distinction between the two receptors in claim 1 a) is unclear. Applicants have not addressed this rejection.

The rejection regarding the use of a "T-cell receptor" that recognizes an antigen together with a "T-cell receptor" that recognizes a cell in the same claim has been withdrawn in view of applicants' arguments.

The rejection of claims 4, 10, 48, 51, 53, 54, 57, 59 has been withdrawn because Hwu described the "MOv-γ" chimeric receptor. It was known to react with an ovarian carcinoma antigen.

The rejection of claim 11 (because it was unclear if the "chimeric receptor reactive with a tumor antigen" may also be the "T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte") has been withdrawn because claim 11 uses similar language as claim 1 to describe the two receptors in the lymphocyte.

The rejection regarding the metes and bounds of the term "MOv-γ" in claims 10, 51, 53 and 57 has been withdrawn. Hwu taught a chimeric receptor made with the V_H and V_K genes of the MOv18 antibody (pg 362, col. 1, "Construction of Chimeric Genes" states the "MOv18 anti-ovarian carcinoma antibody (17, 18) V_H and V_K genes were derived by PCR amplifications using oligodeoxynucleotide primers corresponding to the 5' and 3' consensus amino acid sequences of Ig V regions, and joined together...." This was referred to as the "MOv-γ" chimeric receptor (pg 362, col. 2, 2nd ¶). It is clear that the "MOv-γ" claimed is limited to the "MOv-γ" chimeric receptor described by Hwu that recognizes an ovarian carcinoma antigen.

The rejection regarding the phrase "dual antigen specificity" in claim 41 has been withdrawn in view of the amendment to "dual specificity" (found on pg 11, ¶ 42).

Claim Rejections - 35 USC ' 102

Claims 1, 3, 4, 7, 8, 10, 11, 40, 41 and 44-61 remain rejected and claim 71 is rejected under 35 U.S.C. 102(e) as being anticipated by Nishimura (US Patent 5,830,755) as supported by the definition of "allogeneic" in Dorland's Medical dictionary and the abstract from Shiloni (1993, Cancer Immunology, immunotherapy, Vol. 37, pg 286-292) for reasons of record.

Nishimura taught isolating tumor infiltrating lymphocytes (TIL) from colon adenocarcinoma, stimulating the TIL with antigen and transfecting the cells with a chimeric receptor, Mov-γ, that reacts with ovarian tumors ("38 Tumor") (Example 4, col. 35-39; see ¶ bridging col. 37-38; col. 38, lines 11-13; col. 39, Table 8, "38 Mov-TIL" and

"38 Tumor"). The TIL inherently have an "endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte" because transduced and non-transduced TIL reacted with murine sarcoma cells (24 JK) in an IFN-γ ELISA (col. 39, Table 8; TIL NV and 24 JK).

Interpretation 1: The transduced TIL have two receptors: the MOv-γ chimeric receptor, and a receptor that recognizes the cell line, 24 JK (as evidenced by the results in col. 39, Table 8 (TIL NV and 24 JK)). The 24 JK cell line is "allogeneic" to the TIL of Nishimura. "Allogenic" is defined as "having cell types that are antigenically distinct" (see definition from Dorlands Medical Dictionary provided). JK24 cells are "antigenically distinct" to the transduced TIL because they have low expression of MHC Class I molecules as compared to clone 4JK (see abstract from Shiloni, 1993, Cancer Immunology, immunotherapy, Vol. 37, pg 286-292; lines 3-9).

Interpretation 2: the transduced TIL have two receptors: the MOv-γ chimeric receptor, and an endogenous T-cell receptor that recognizes an allogeneic cell. The second receptor is inherent in the population of transduced TIL described by Nishimura because a population of TIL has a diverse array of endogenous T-cell receptors. One of the many endogenous T-cell receptors present in the population of transduced TIL must recognize at least one allogeneic cell. Therefore, the TIL of Nishimura inherently have an endogenous receptor that recognizes allogeneic cells. For example, the TIL inherently have endogenous T-cell receptors that recognize mouse, human or plant cells.

Interpretation 3: the transduced TIL have two receptors: the MOv-γ chimeric receptor and an endogenous T-cell receptor that recognizes the antigen with which the TIL are stimulated. The TIL are exposed to an antigen prior to transduction to stimulate growth and expansion of cells that recognize the antigen, i.e. have an endogenous T-cell receptor recognizing the antigen.

The steps taught by Nishimura are equivalent to the steps of claim 41.

Nishimura taught human TIL could be transduced and used in the invention (col. 38, lines 55-65), which is equivalent to claims 45, 47, 52 and 61.

Applicants argue the TIL were not transduced. Applicants' argument is not persuasive. Col. 37, lines 54-60, expressly taught transducing the cells with a vector encoding the chimeric Mov-γ receptor. The transduced TIL inherently have a receptor that reacts with allogeneic cells 24 JK because both transduced and non-transduced TIL released INF-γ upon being in contact with 24 JK (col. 39, Table 8, TIL NV, TIL-Moγ and 24 JK).

Applicants argue the chimeric Mov-γ receptor cannot also be construed as the second "endogenous" receptor (interpretation 2). Applicants state "Mov-γ receptor is a *chimeric* receptor, meaning that it is not endogenous to the TIL." Applicants' argument is moot. This interpretation has been withdrawn in view of the response to the 112/2nd rejection above.

Applicants argue the examiner has not supported the position that TIL inherently have receptors that recognize allogeneic cells. Applicants argue that inherency may not be relied upon using probabilities or possibilities. Applicants' argument is not

persuasive. Shilyansky of record (PNAS, March 1994, Vol. 91, pg 2829-2833), explicitly refers to the T-cell receptor repertoire of TIL as "diverse". Nishimura (J. Immunotherapy, Vol. 16, pg 85-94) of record. One of the many and diverse T-cell receptors in a population of TIL must recognize an allogeneic cell. Nishimura expressly taught the TIL recognized allogeneic cell line 24 JK. The TIL were stimulated with an antigen; therefore, the TIL must recognize allogeneic cells expressing that antigen.

Applicants state, "the TIL disclosed in the '755 patent were stimulated by an antigen (see col. 36, line 44) and it is this antigen to which the endogenous receptor should react." Applicants' argument is not persuasive. The claims do not exclude TIL that are stimulated by an antigen or TIL having an endogenous receptor that recognizes an antigen after stimulation with the antigen. The transduced TIL taught in '755 have two receptors, the chimeric Mov-γ receptor and an endogenous receptor that recognizes an allogeneic cell, which is all that is required for the claims.

Applicants argue '755 does not contact the transduced TIL with an allogeneic cell. Applicants' argument is not persuasive. The products of claims 1, 4, 7, 8 10, 41-56 and 71 do not require contacting allogeneic cells. The step of contacting lymphocytes with allogeneic cells in claim 41 is met because Nishimura clearly showed contacting the transduced TIL with 24 JK, an allogeneic cell line (Col. 39, Table 8).

Claims 1, 3, 7, 8, 11, 40, 41, 45-47, 50, 52, 56, 58 and 61 remain rejected and claim 71 is rejected under 35 U.S.C. 102(e) as being anticipated by Capon (US Patent 6,407,221, June 18, 2002, filed 6-7-95).

Capon taught a primary human CD8+ lymphocyte transduced with a vector encoding a chimeric receptor that recognizes a tumor antigen (col. 5, lines 26-29; col. 11, lines 41-44; col. 11, line 66, through col. 12, line 8; col 12, line 40; col. 31, line 37-44; claim 2). In addition, Capon used the HIV protein gp120 as an antigen in tumor cells; therefore, the gp120 protein is a "tumor antigen" in the teachings of Capon.

The transformed population of cells taught by Capon inherently has a second receptor that is an endogenous T-cell receptor reactive with a cell that is allogeneic to the lymphocyte. The lymphocytes taught by Capon inherently have a wide array of T-cell receptors and, therefore, must inherently have endogenous receptors that recognize cells from a human having a different MHC genetic background. Non-transduced primary human CD8+ lymphocytes would recognize any human cell that had a different MHC molecule, including PBMC, dendritic cells and splenocytes (claims 8, 46, 50, 56, 58). Therefore, the gene-modified primary human CD8+ lymphocytes would also recognize any human cell that had a different MHC molecule.

Applicants argue the disclosure of '221 does not support the examiner's inherency argument. Applicants argue the chance that one of the transduced lymphocytes of '221 has an endogenous T-cell receptor that is reactive to an allogeneic cell is not an inherent feature of the cells (the logic in this aspect of the argument is a little unclear). Applicants' argument is not persuasive because the abstracts of

Shilyansky of record (PNAS, March 1994, Vol. 91, pg 2829-2833) and Nishimura (J. Immunotherapy, Vol. 16, pg 85-94) of record explicitly refer to the T-cell receptor diversity of TIL as "diverse". See also Cole (Cancer Res. 1997, Vol. 47, pg 5320-5327) who taught that the T-cell repertoire of TIL was diverse.

Claims 1, 3, 7, 8, 11, 40, 41, 45-47, 50, 52, 56, 58 and 61 remain rejected and claim 71 is rejected under 35 U.S.C. 102(e) as being anticipated by Capon (US Patent 5,359,046, Oct. 25, 1994, filed 12-9-92) for reasons of record.

Capon taught a primary human CD8+ lymphocyte transduced with a vector encoding a chimeric receptor that recognizes a tumor antigen (col. 11, lines 48-56; col. col. 12, line 7-16; col 12, line 45-52; claim 6). In addition, Capon used the HIV protein gp120 as an antigen in tumor cells; therefore, the gp120 protein is a "tumor antigen" in the teachings of Capon.

The transformed population of cells taught by Capon inherently has a second receptor that is an endogenous T-cell receptor reactive with a cell that is allogeneic to the lymphocyte. The lymphocytes taught by Capon inherently have a wide array of T-cell receptors and, therefore, must inherently have endogenous receptors that recognize cells from a human having a different MHC genetic background. Non-transduced primary human CD8+ lymphocytes would recognize any human cell that had a different MHC molecule, including PBMC, dendritic cells and splenocytes (claims 8, 46, 50, 56, 58). Therefore, the gene-modified primary human CD8+ lymphocytes would also recognize any human cell that had a different MHC molecule.

Applicants argue the disclosure of '046 does not support the examiner's inherency argument. Applicants argue the chance that one of the transduced lymphocytes of '046 has an endogenous T-cell receptor that is reactive to an allogeneic cell is not an inherent feature of the cells (the logic in this aspect of the argument is a little unclear). Applicants' argument is not persuasive because the abstracts of Shilyansky of record (PNAS, March 1994, Vol. 91, pg 2829-2833) and Nishimura (J. Immunotherapy, Vol. 16, pg 85-94) of record explicitly refer to the T-cell receptor diversity of TIL as "diverse". See also Cole (Cancer Res. 1997, Vol. 47, pg 5320-5327) who taught that the T-cell repertoire of TIL was diverse.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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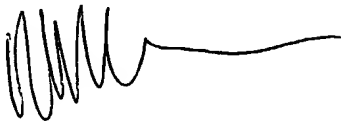
For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER